

Neural Correlates of Alcohol-Approach Bias in Alcohol Addiction: the Spirit is Willing but the Flesh is Weak for Spirits

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Behavioral studies have shown an alcohol-approach bias in alcohol-dependent patients: the automatic tendency to faster approach than avoid alcohol compared with neutral cues, which has been associated with craving and relapse. Although this is a well-studied psychological phenomenon, little is known about the brain processes underlying automatic action tendencies in addiction. We examined 20 alcohol-dependent patients and 17 healthy controls with functional magnetic resonance imaging (fMRI), while performing an implicit approach-avoidance task. Participants pushed and pulled pictorial cues of alcohol and soft-drink beverages, according to a content-irrelevant feature of the cue (landscape/portrait). The critical fMRI contrast regarding the alcohol-approach bias was defined as (approach alcohol > avoid alcohol) > (approach soft drink > avoid soft drink). This was reversed for the avoid-alcohol contrast: (avoid alcohol > approach alcohol) > (avoid soft drink > approach soft drink). In comparison with healthy controls, alcohol-dependent patients had stronger behavioral approach tendencies for alcohol cues than for soft-drink cues. In the approach, alcohol fMRI contrast patients showed larger blood-oxygen-level-dependent responses in the nucleus accumbens and medial prefrontal cortex, regions involved in reward and motivational processing. In alcohol-dependent patients, alcohol-craving scores were positively correlated with activity in the amygdala for the approach-alcohol contrast. The dorsolateral prefrontal cortex was not activated in the avoid-alcohol contrast in patients vs controls. Our data suggest that brain regions that have a key role in reward and motivation are associated with the automatic alcohol-approach bias in alcohol-dependent patients.

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INTRODUCTION

Addiction is characterized by habitual drug use, despite negative consequences, and by high rates of relapse, even though the addicted person is often aware of the harm (Stacy and Wiers, 2010). Recent theories suggest reward-related learning to be important for the development of addiction (Hyman *et al*, 2006; Wrase *et al*, 2002): a transition occurs from voluntary to impulsive use, in which cues associated with the drug increase in incentive salience

(Robinson and Berridge, 1993, 2003). Drug cues then automatically trigger drug-like approach responses (Robinson and Berridge, 1993, 2003). Dual process models of addiction propose an imbalance between these strong automatic 'approach'-oriented processes and a suboptimal functioning of cognitive control processes (Bechara, 2005; Gladwin *et al*, 2011). This imbalance may explain the paradoxical conflict that characterizes addiction: urges to take the drug that the individual fails to control despite an explicit desire to quit.

Previous research has demonstrated that drug-dependent individuals exhibit an automatically activated tendency to approach rather than to avoid drug cues relative to neutral cues (ie, drug approach bias; Cousijn *et al*, 2011; Ernst *et al*, 2012; Wiers *et al*, 2013; Zhou *et al*, 2012). The drug approach bias is likely to reflect an embodied motor reaction towards drug cues and has been positively related

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to subjective rates of drug craving (Wiers *et al*, 2013). Moreover, bias modification training schemes, in which drug users learn to avoid drug cues in a joystick paradigm, have been shown to reduce relapse rates up to 13% in alcohol-dependent patients 1 year after training (Eberl *et al*, 2012; Wiers *et al*, 2011). These findings highlight the clinical relevance of approach bias in drug use. However, neural correlates associated with the drug approach bias remain largely unknown.

The incentive sensitization theory of addiction suggests fronto-limbic neuroadaptations to underlie the drug approach bias (Robinson and Berridge, 2003). Many drugs of abuse (eg, alcohol, nicotine, or cocaine) directly or indirectly trigger the release of dopamine from the ventral tegmental area, projecting to fronto-limbic structures such as the nucleus accumbens (NAcc) and medial prefrontal cortex (mPFC; Heinz *et al*, 2009; Hyman and Malenka, 2001). As dopamine signals motivational relevance with every puff, drink, or shot, Pavlovian-conditioned associations between drug cues and reward are formed and encoded in the amygdala (Baler and Volkow, 2006; Heinz *et al*, 2009). In this way, drug cues acquire incentive sensitization and consequently engender approach behavior (Robinson and Berridge, 1993, 2003).

Human functional magnetic resonance imaging (fMRI) studies have shown that when drug users passively view drug cues, blood-oxygen-level-dependent (BOLD) signal (hereafter referred to as activity) in the fronto-limbic reward circuit increases (Heinz *et al*, 2009; Schacht *et al*, 2013). Key brain areas that activate in drug users are the NAcc, mPFC, dorsolateral prefrontal cortex (dlPFC), and amygdala (Heinz *et al*, 2009; Schacht *et al*, 2013). However, despite the evidence for fronto-limbic involvement in drug-cue reactivity, the precise role of these areas remains unclear. The NAcc, mPFC, and amygdala have been associated with bottom-up motivational aspects of cue reactivity (Braus *et al*, 2001; Hare *et al*, 2009; Heinz *et al*, 2009; Wrase *et al*, 2007), reward processing (Kahnt *et al*, 2010; Koob and Volkow, 2010; Park *et al*, 2011), subjective drug craving, and relapse (Beck *et al*, 2012; Childress *et al*, 1999; Grusser *et al*, 2004; Hayashi *et al*, 2013; Heinz *et al*, 2004; Volkow *et al*, 2004). The dlPFC has been shown to be structurally and functionally impaired in drug addiction, and may be related to suboptimal cognitive control (Baler and Volkow, 2006; Bechara, 2005; Hayashi *et al*, 2013; Jentsch and Taylor, 1999; Park *et al*, 2010). Previous approach/avoidance studies on emotional processing showed that dlPFC is more active when stimulus and response are incongruent (approach sad faces) than congruent (approach happy faces; Roelofs *et al*, 2009; Volman *et al*, 2011). If patients indeed have an alcohol-approach bias (congruent), the dlPFC would be expected to be active while avoiding alcohol cues (incongruent). Alternatively, when patients lack the control to avoid alcohol cues, one would expect decreased dlPFC activation for avoiding alcohol cues. How these antagonistic processes of motivation and control underlie automatic approach tendencies for alcohol as yet remains unknown.

In the current study, we measured the neural correlates of the automatic alcohol-approach bias using fMRI. Abstinent alcohol-dependent patients and healthy controls performed an implicit approach-avoidance task (AAT) in an fMRI

scanner. As such, this is the first study that investigates the neural correlates of the alcohol-approach bias in alcohol dependence using fMRI. Participants pushed and pulled pictorial cues of alcohol and soft-drink beverages using a joystick. Compared with controls, patients were hypothesized to faster pull than push alcohol stimuli compared with soft-drink stimuli. For the fMRI alcohol-approach bias interaction (approach alcohol > avoid alcohol) > (approach soft drink > avoid soft drink), we expected increased activity in the NAcc, mPFC, and amygdala, areas previously associated with reward and motivational processing. Subjective craving scores of alcohol-dependent patients were hypothesized to correlate positively with the alcohol-approach bias-related activity in these regions. Lastly, we investigated whether patients showed either greater or reduced dlPFC activity than healthy controls in a reverse avoid-alcohol contrast (avoid alcohol > approach alcohol) > (avoid soft drink > approach soft drink), indicating enhanced or reduced inhibitory control, respectively.

MATERIALS AND METHODS

Participants and Instruments

The Ethical Committee of the Charité, Universitätsmedizin Berlin, approved the study. Thirty-seven right-handed male subjects participated: 20 alcohol-dependent in-patients ($M = 44.3$ years ($SD = 7.98$), range = 26–55) and 17 healthy control subjects ($M = 42.1$, $SD = 8.32$, range = 22–53). The groups did not differ in mean age and years of education (Table 1). Controls were recruited via online advertisements. Exclusion criteria for all participants were a history of neurological dysfunctions, axis I psychiatric disorders according to DSM-IV criteria other than alcohol dependence in the alcohol-dependent group (M.I.N.I. plus, an International Neuropsychiatric Interview; Sheehan *et al*, 1998), and intake of psychoactive medication. Controls did not fulfill criteria of (a history of) drug abuse and dependence, except tobacco. For controls, potential participants with scores above 8 on the Alcohol Use Disorder Identification Test (Saunders *et al*, 1993) were excluded, as screened in a telephone interview before the experiment. Patients were recently detoxified (<6 months; $M = 53.40$ days, $SD = 49.51$), had been suffering from alcohol dependence for 16.6 ($SD = 8.5$ years, range 1–30), underwent 3.9 ($SD = 6.7$) previous detoxifications (range 0–25), and scored 16.4 ($SD = 8.4$) on the Alcohol Dependence Scale (Skinner and Allen, 1982). Smokers were abstinent from tobacco at least 1.5 h before scanning, in order to decrease direct effects of nicotine on the BOLD signal (Jacobsen *et al*, 2002). All patients expressed the desire to remain abstinent from alcohol.

In order to assess lifetime history of alcohol and drug abuse for both groups, we interviewed participants on the Life Time Drinking History scale (Skinner and Sheu, 1982). Alcohol craving was assessed with the Desire for Alcohol Questionnaire (DAQ; Love *et al*, 1998). Furthermore, participants completed Matrix Reasoning of the Wechsler Adult Intelligence scale (Kaufman and Lichtenberger, 2006) as a proxy for general intelligence and the Spielberger's State-Trait Anxiety Questionnaire (STAI) to evaluate state and trait anxiety (Spielberger *et al*, 1983).

Table 1 Demographic and Clinical Data of Alcohol-Dependent Patients and Healthy Controls

	Alcohol-dependent patients (n = 20, all male)	Healthy controls (n = 17, all male)	P-value
Age (years)	44.30 (7.98)	42.12 (8.3)	0.422 NS
BMI	23.98 (3.43)	24.44 (2.33)	0.637 NS
Years of education	10.55 (1.15)	11.29 (1.72)	0.141 NS
WAIS matrices score	15.21 (4.43)	17.24 (6.13)	0.260 NS
STAI-T	36.00 (8.30)	34.24 (12.09)	0.630 NS
STAI-S	32.95 (8.20)	32.24 (7.09)	0.780 NS
DAQ	14.30 (6.73)	4.88 (4.43)	0.000***
Lifetime alcohol intake (kg)	2052.74 (2821.01)	153.62 (225.92) ^a	0.007***
AUDIT	27.05 (7.82)	2.82 (1.67)	0.000***
ADS	16.43 (8.04) ^b	—	—
Abstinence (days)	53.40 (49.51)	—	—
Number of detoxifications	3.90 (6.72)	—	—
Duration of dependence (years)	16.55 (8.52)	—	—

Abbreviations: ADS, Alcohol Dependence Scale; AUDIT, Alcohol Use Disorders Test; BMI, body mass index; DAQ, Desire for Alcohol Questionnaire; NS, not significant; STAI-S, State Anxiety Inventory; STAI-T, Trait Anxiety Inventory; WAIS, Wechsler Adult Intelligence Scale.

*** $p < 0.001$.

^a $N = 16$.

^b $N = 19$.

AAT Description and Subjective Rating

A zoom version of the AAT, optimized for MRI, was used (Figure 1). Participants pushed or pulled an MRI-compatible joystick (Fiber Optic Joystick, Current Designs), in response to the format of the cue (landscape or portrait). After 20 practice trials, 160 test trials were presented over 4 blocks, in which each picture was approached and avoided once. Picture format to response assignment was counter-balanced, with half of the participants pulling the joystick for landscape and pushing it for portrait cues, and vice versa. For optimal approach and avoidance resemblance (Rinck and Becker, 2007), the AAT used here was developed with a zooming feature: moving the joystick increased and decreased the size of the cue. Participants had to respond to a picture within 2 s. Intertrial intervals were 4, 6, or 8 s distributed hyperbolically (Miezin *et al*, 2000). A set of 40 alcohol and 40 soft-drink images was used, previously matched for drink familiarity and for arousal in an independent male, social drinking German sample ($N = 20$). Images (660×660 pixels) were presented in a white frame (900×660 pixels landscape and 660×900 pixels portrait format), against a black background. The task was programmed in MATLAB (r2010a; MathWorks Company) and Psychtoolbox v3 (Brainard, 1997). After scanning, all pictures were rated for familiarity ('How familiar is this drink to you?'), arousal ('How much does this drink move you?'), and valence ('How positive or negative is this drink to you?'), on a five-point Likert scale.

fMRI Acquisition and Preprocessing

Stimuli were presented in an event-related design (4 runs of 40 trials) in a 3 T MRI scanner (MAGNETOM Trio, TIM-Technology; Siemens, Erlangen, Germany), equipped with a

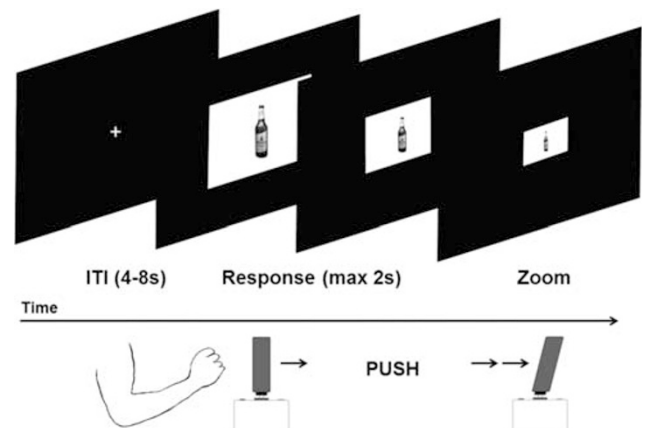


Figure 1 Schematic overview of an avoid alcohol trial on the approach-avoidance task (AAT), in which the cue zooms out while pushing on the joystick.

12-channel head coil. A standard T2-weighted echo planar imaging (EPI) sequence was used with the following parameters: descending, repetition time 2 s, echo time 25 ms, flip angle $\alpha 80^\circ$, 64×64 pixels in-plane resolution, 34 slices, slice thickness 3 mm, voxel dimensions $3 \times 3 \times 3 \text{ mm}^3$, with a 0.75-mm gap between slides, and field of view $192 \times 192 \text{ mm}^2$. In each of the 4 runs, 163 images were acquired. To improve functional sensitivity in the mPFC, the acquisition plane was tilted 25° clockwise from anterior-posterior commissure (Deichmann *et al*, 2003).

Functional data analysis was performed with SPM8 (Wellcome Department of Cognitive Neurology, London, UK). During preprocessing, scans were spatially realigned, slice-time corrected and normalized to the standard

Montreal Neurological Institute (MNI) EPI template. Smoothing was performed with an 8-mm full-width at half-maximum Gaussian kernel. None of the participants moved more than 2 mm or 2° within runs.

Statistical Analysis

Responses that were missed or incorrect and response times (RTs) longer than 3 SDs above the mean were discarded based on each participant's performance. RTs were computed as the time required from the onset of stimulus presentation until the joystick reached a maximum or minimum position. Approach tendencies were calculated by subtracting median RT scores of pushing minus pulling pictures for each drink type. Positive approach tendencies indicate faster approaching than avoiding an image type, whereas negative approach tendencies indicate faster avoidance than approach. A 2 × 2 mixed ANOVA on approach tendencies was calculated, with drink type (alcohol/soft drink) as the within-subject factor and group (alcohol-dependent/healthy control) as the between-subject factor. *Post-hoc* group comparisons on separate approach tendencies (alcohol/soft drink) were performed with two-sided two-sample Student's *t*-tests. The behavioral alcohol-approach bias RT score was defined as the difference score of approach tendency for alcohol minus approach tendency for soft drink. Pearson's correlation was calculated between the behavioral alcohol-approach bias and DAQ alcohol craving.

For fMRI data, there were five regressors per subject: alcohol push, alcohol pull, soft-drink push, soft-drink pull, and missed trials. Single trials were modeled with the trial's RT as duration of the event and convolved with the hemodynamic response function. The six realignment parameters were included as regressors of no interest. Temporal filtering of 128 s was used.

The following contrasts were calculated per subject: (1) (approach alcohol > avoid alcohol) > (approach soft drink > avoid soft drink) for the approach-alcohol contrast and (2) the reverse (avoid alcohol > approach alcohol) > (avoid soft drink > approach soft drink) for the avoid-alcohol contrast. On the second level, both contrasts were compared between groups using a two-sample Student's *t*-test. We created four regions of interest (ROIs), based on our *a priori* hypotheses (Figure 2). Both the NAcc and amygdala ROIs were defined by the bilateral NAcc and amygdala using the human anatomical WFU Pickatlas (Maldjian *et al*, 2003). As mPFC and bilateral dlPFC are anatomically not clearly defined, two functional ROIs of these brain areas were downloaded from an online atlas of functional ROIs (Shirer *et al*, 2012). ROIs were used for small-volume correction (SVC) of the results, with a significance threshold of $p < 0.05$, family-wise error corrected (FWE).

For *post-hoc* analyses, two approach tendency contrasts were calculated on the first level: (1) (approach alcohol > avoid alcohol) and (2) (approach soft drink > avoid soft drink). These contrasts were compared between groups using two-sample Student's *t*-tests, masked with our *a priori* defined ROIs.

To test whether length of abstinence was negatively related to activity in our ROIs, regression analyses within

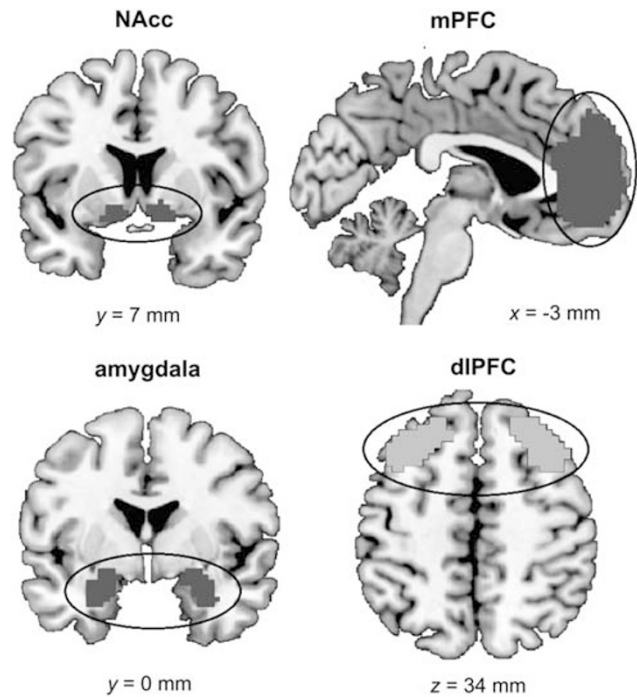


Figure 2 *A-priori* defined regions of interests of the motivational system (nucleus accumbens (NAcc), medial prefrontal cortex (mPFC), and amygdala) and of the cognitive control system (dorsolateral prefrontal cortex (dlPFC)), shown in red and blue respectively.

these ROIs with length of abstinence as a regressor were performed in alcohol-dependent patients only.

To identify correlations with DAQ craving scores and alcohol-approach bias-related brain activations in alcohol-dependent patients, we performed a regression analysis on the approach-alcohol contrast, with DAQ scores as a regressor. Results of correlations were FWE corrected (SVC) for our ROIs (NAcc, mPFC, and amygdala).

RESULTS

Behavioral Assessment and Subjective Ratings

Groups did not differ in years of education, body mass index, Wechsler Adult Intelligence Scale intelligence scores, or in anxiety trait (STAI-T) and state (STAI-S) scores (Table 1). There were more smokers in the alcohol-dependent group ($N = 20$, 100%) compared with the control group ($N = 6$, 28.3%; $\chi^2 = 7.54$, $p = 0.006$). However, we did not include smoking as a covariate, as smoking behavior was related to lifetime alcohol consumption ($R = 0.58$, $p = 0.007$; also when corrected for age: $R = 0.58$, $p = 0.007$) and DAQ craving scores ($R = 0.45$, $p = 0.047$) in alcohol-dependent patients. Consequently, including smoking as a covariate may remove variance explained by drinking behavior (an exploratory analysis with smoking behavior as a covariate in the main group analysis revealed that whereas results on the NAcc ($p < 0.05$, FWE) and dlPFC (lack of effect at $p > 0.05$, FWE) in both the approach and avoid contrast did not change, activity in the mPFC did not reach significance when including smoking as a covariate ($p > 0.05$, FWE)).

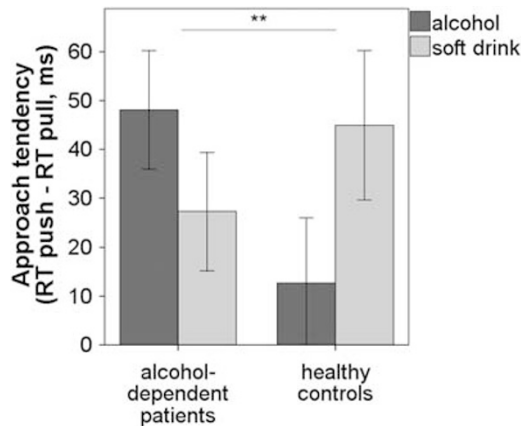


Figure 3 Mean approach tendencies (response time (RT) avoid—approach) for alcohol and soft-drink cues. There was a significant interaction effect of drink type \times group ($p < 0.01$), with alcohol cues being approached faster in alcohol-dependent patients as a trend ($p < 0.06$). Error bars depict 1 SE above and below the mean. ** $p < 0.01$.

DAQ alcohol-craving ratings were higher in alcohol-dependent patients ($M = 14.3$, $SD = 6.7$) compared with healthy controls ($M = 4.88$, $SD = 4.4$; $t(35) = 3.55$, $p = 0.001$). Picture ratings (familiarity, valence, and arousal) for both alcohol and soft-drink cues did not differ between groups (all $p > 0.13$).

For the AAT, all RT variables, both separate approach tendencies (alcohol/soft drink) and the overall alcohol-approach bias score were distributed normally (Kolmogorov–Smirnov test: all $p > 0.12$). The assumption of homogeneity of variance was met in all cases (Levene’s test for equality of variance: all $p > 0.52$). Mean error rate was 1.71% ($SD = 1.95$) and error rates did not differ between groups ($t(35) = 0.49$, $p = 0.63$).

As hypothesized, for behavioral approach tendencies there was a significant interaction effect between drink type \times group ($F(1,34) = 9.99$, $p = 0.003$, $\eta^2 = 0.22$; Figure 3). *Post-hoc* Student’s *t*-tests revealed that patients had greater approach tendencies for alcohol cues ($M = 48.10$ ms, $SD = 54.35$) compared with healthy controls by trend ($M = 12.71$ ms, $SD = 54.61$; $t(35) = 1.97$, $p = 0.057$). In contrast, approach tendencies for soft-drink cues did not differ between groups ($t(35) = -0.92$, $p = 0.37$).

The behavioral alcohol-approach bias did not correlate with DAQ alcohol-craving scores, either in alcohol-dependent patients ($r = 0.17$, $p = 0.48$) or in healthy controls ($r = -0.18$, $p = 0.49$).

fMRI Results

Approach alcohol. For the main contrast of interest (approach alcohol $>$ avoid alcohol) $>$ (approach soft drink $>$ avoid soft drink), alcohol-dependent patients showed a higher BOLD response in the NAcc area (peak in MNI space [x, y, z] = [15, 5, -8]); $t = 3.54$, $p < 0.05$, FWE) and the mPFC (peak = [0, 59, 7]); $t = 4.43$, $p < 0.05$, FWE) compared with that in healthy controls (Figure 4). The amygdala was not more strongly activated in patients compared with controls (bilateral; $p > 0.05$, FWE), even at a more liberal threshold of $p < 0.005$ uncorrected. Although the dlPFC was not more activated in patients than in controls with a threshold of

$p < 0.05$, FWE, a cluster in the left dlPFC survived the exploratory, a more liberal threshold of $p < 0.005$ uncorrected.

Post-hoc Student’s *t*-tests on separate approach tendency contrasts revealed that alcohol-related activity (approach alcohol $>$ avoid alcohol) did not differ between groups in the NAcc and mPFC ($p > 0.005$ uncorrected). Approach tendency-related activity for soft-drink cues (approach soft drink $>$ avoid soft drink) was larger in healthy controls than in alcohol-dependent patients, both in the NAcc (peak = [9, 8, -8]; $t = 3.08$, $p < 0.05$, FWE) and mPFC (peak = [-12, 56, 7]); $t = 5.15$, $p < 0.05$, FWE).

Within patients, length of abstinence was not correlated with the approach-alcohol contrast within our ROIs ($p > 0.05$, few, and $p > 0.005$, uncorrected).

Avoid alcohol. In the reverse avoid-alcohol contrast (avoid alcohol $>$ approach alcohol) $>$ (avoid soft drink $>$ approach soft drink), no suprathreshold activity was reached in the dlPFC (bilateral; $p > 0.05$, FWE) in patients versus controls. Moreover, an additional analysis with a more liberal threshold of $p < 0.005$ (uncorrected) did not reveal suprathreshold activity.

Correlation of craving scores with alcohol-approach bias-related activity in alcohol-dependent patients. Alcohol-dependent patients’ DAQ craving scores correlated positively with activity in the amygdala for the approach-alcohol contrast (peak = [30, -7, -11]); $t = 4.25$, $p < 0.05$, FWE; Figure 5). There were no positive correlations between alcohol craving and activity in the NAcc or mPFC, even at $p < 0.005$ uncorrected.

Results of whole brain-analyses are reported in Supplementary Table S1.

DISCUSSION

The current study shows that in comparison with healthy controls, alcohol-dependent patients had stronger behavioral approach tendencies for alcohol cues than for soft-drink cues. At the neural level, the alcohol-approach bias interaction of drink type (alcohol *vs* soft drinks) \times movement (approach *vs* avoid) was associated with stronger brain response in both the NAcc and mPFC, areas that have previously been shown to have a role in alcohol cue reactivity, reward processing, and the motivational value of stimuli (Grusser *et al*, 2004; Hare *et al*, 2009; Heinz *et al*, 2009; Kahnt *et al*, 2010; Park *et al*, 2011). Here we show that these areas are more active in patients *vs* controls while approaching *vs* avoiding alcohol cues, relative to soft-drink cues. This extends previous studies, which mostly involved passive viewing of alcohol cues (Heinz *et al*, 2009; Schacht *et al*, 2013). However, no strong effects were found in the dlPFC. Thus, we did not find direct support for enhanced or decreased neural inhibitory control, while patients were avoiding alcohol. The results suggest that differences in the motivational reward system, rather than a less active control system, underlie automatic action tendencies to alcohol in alcohol dependence.

The main findings support incentive sensitization models of addiction that propose fronto-limbic neuroadaptations to

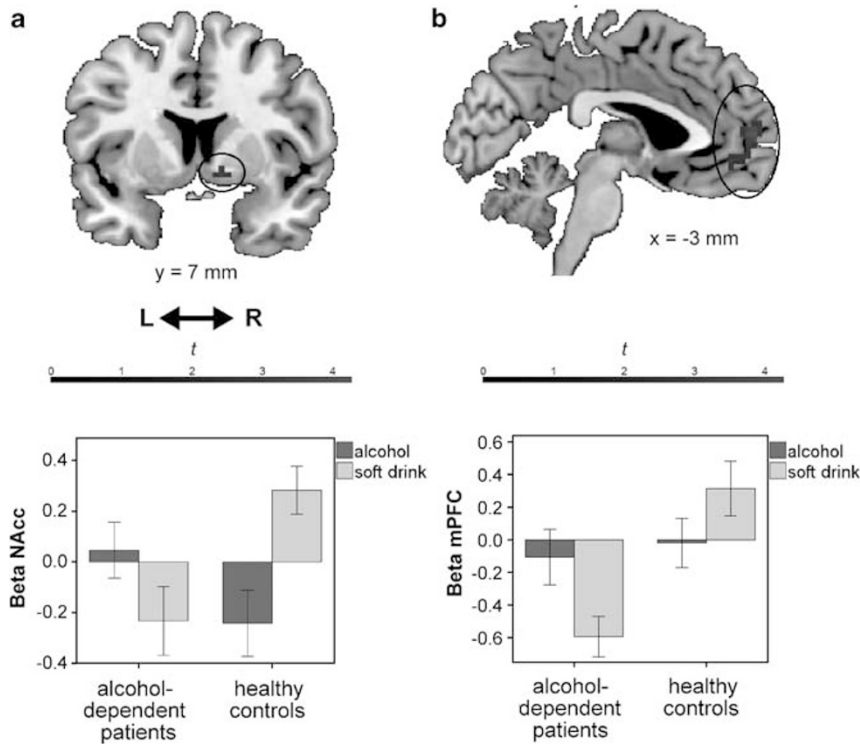


Figure 4 Nucleus accumbens (NAcc; a) and medial prefrontal cortex (mPFC; b) showed higher blood-oxygen-level-dependent (BOLD) response in alcohol-dependent patients compared with healthy controls in the alcohol-approach bias contrast (approach alcohol > avoid alcohol) > (approach soft drink > avoid soft drink). The effects were significant at $p < 0.05$ (family-wise error (FWE) corrected and small-volume correction (SVC)). For visualization, activations within our NAcc regions of interest (ROI; a) and our mPFC ROI (b) are plotted with a threshold of $p < 0.005$ uncorrected, on a standard anatomical brain template using MRICron software. Bar plots of mean β -values per stimulus category (alcohol/soft drink) and per group (extracted from all voxels that were active at $p < 0.005$ uncorrected) are for visualization purposes only. As performing *post-hoc* tests on these extracted β -values would be considered double dipping (Kriegeskorte *et al*, 2010), *post-hoc* Student's *t*-tests on separate approach tendency contrasts were performed using our a-priori NAcc and mPFC ROIs. These revealed that there were no group differences in approach tendency-related activity for alcohol (approach alcohol > avoid alcohol; $p > 0.005$ uncorrected). In contrast, approach tendency-related activity for soft drinks (approach soft drink > avoid soft drink) was larger in healthy controls than alcohol-dependent patients, both in the NAcc ($p < 0.05$, FWE) and mPFC ($p < 0.05$, FWE).

underlie the automatic approach bias to drug cues in addicted individuals (Robinson and Berridge, 1993, 2003). The NAcc has been shown to be responsive to alcohol cue reactivity in alcohol-dependent patients (Braus *et al*, 2001; Heinz *et al*, 2009; Wrase *et al*, 2007) and regulates drug sensitization in animals (Abraham *et al*, 2011). The mPFC is hypothesized to code subjective value signals important for goal-directed decision making (Hare *et al*, 2009; Kahnt *et al*, 2010; Park *et al*, 2011) and has been related to the attribution of incentive salience to alcohol cues (Grusser *et al*, 2004). Recently, activity in the mPFC was shown for the cannabis approach bias in both cannabis users and non-smoking controls (Cousijn *et al*, 2012). Moreover, a recent near-infrared spectroscopy study demonstrated that the neighboring orbitofrontal cortex is active when alcohol-dependent patients approach alcohol cues (Ernst *et al*, 2012). Hence, the NAcc and mPFC may have important roles in the drug approach bias.

As expected, alcohol-dependent patients reported higher subjective craving for alcohol when compared with the control group. Although the amygdala was not activated in the main approach-alcohol contrast in patients *vs* controls, alcohol-approach bias-related brain activity in the amygdala correlated positively with alcohol-craving scores in patients. This finding is in line with previous neuroimaging findings

that also showed a positive relation between activity in the amygdala while passively viewing alcohol cues and subjective craving (Childress *et al*, 1999; Koob and Volkow, 2010). The amygdala has a key role in Pavlovian-conditioned learning, and the formation and consolidation of emotional memories (Koob and Volkow, 2010; Volkow *et al*, 2004). Drug craving may therefore lead to increased memories of the abused drug or, in reverse, approaching alcohol may trigger drug associations and memories that initiate craving. However, our results did not support the hypotheses that increased NAcc and mPFC were related to subjective craving in patients. It may therefore be that NAcc and mPFC are specific for automatic approach reactions rather than explicit subjective judgments of drug craving, whereas the amygdala is only activated in patients that are explicitly aware of their craving.

The dlPFC was neither more nor less active in our avoid-alcohol contrast in patients *vs* controls, under the stringent threshold of $p < 0.05$, FWE. More activity in the dlPFC was expected in patients compared with controls, as previous studies found that the dlPFC is generally more active when stimulus and response are incongruent (Roelofs *et al*, 2009; Volman *et al*, 2011). In contrast, it may be that patients lack control to avoid alcohol and hence show reduced dlPFC activity in the avoid-alcohol contrast. In the latter contrast,

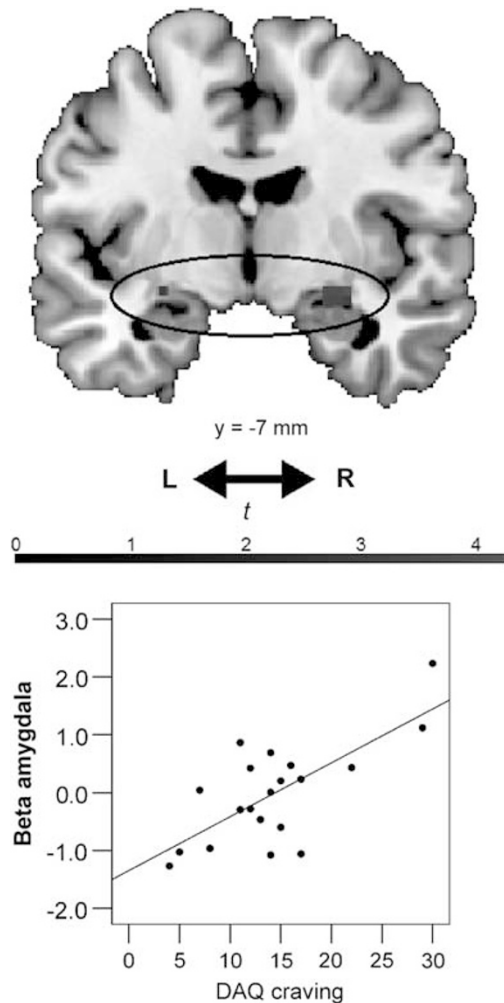


Figure 5 Craving scores correlated positively with alcohol-approach bias-related brain activity in the amygdala in alcohol-dependent patients ($p < 0.05$, family-wise error (few) corrected and small-volume correction (SVC)). Activations within the amygdala regions of interest (ROI) are plotted here on a standard anatomical brain template using MRICron software, with a threshold of $p < 0.005$ uncorrected. Mean β -values were extracted from the activated clusters within the amygdala ROI (at $p < 0.005$ uncorrected), in order to produce the correlation plot. The correlation plot is for visualization purposes only. No further *post-hoc* tests were performed on these extracted data, as this would be considered double dipping (Kriegeskorte *et al*, 2010).

a cluster in the left dlPFC survived the exploratory, more liberal threshold of $p < 0.005$ uncorrected. As this result is uncorrected only, it cannot be firmly interpreted. Thus, differences in dlPFC activation between groups cannot be excluded at this point (and neither can they be confirmed). As alcohol-dependent patients were all clinic in-patients, it may be that avoiding alcohol cues was not incongruent for this population. This could explain why the dlPFC was not activated in the avoid-alcohol contrast in patients compared with controls. Future studies could investigate whether neural correlates of the alcohol-approach bias in social or hazardous drinkers for whom drinking is not (yet) problematic would involve dlPFC activity for avoiding alcohol. Moreover, in high-risk cannabis smokers, higher dlPFC activity during cannabis approach trials but lower

activity during cannabis avoidance trials were associated with decreases in cannabis problem severity 6 months later (Cousijn *et al*, 2012). Although these findings were obtained with a structurally different task, in which participants symbolically approach the drug in certain mini-blocks and avoid it in other mini-blocks, future studies could focus on alcohol-approach bias-related dlPFC activity in relation to future addiction severity in alcohol dependence.

Post-hoc Student's *t*-tests revealed that the significant behavioral alcohol-approach bias interaction was mainly driven by a trend-wise difference between groups in approach tendencies for alcohol cues rather than soft-drink cues. That is, as hypothesized, behavioral approach tendencies for alcohol were larger in patients *vs* controls, whereas there was no detectable group difference for soft-drink approach tendencies. In contrast, the interaction of BOLD responses in mPFC and NAcc was mainly driven by group differences in approach > avoid soft-drink cues rather than approach > avoid-alcohol cues. That is, patients showed significantly lower activity in the mPFC and NAcc when approaching > avoiding soft drinks, but there were no significant between-group differences in BOLD responses when approaching > avoiding alcohol. It is, however, difficult to interpret the separate approach tendency contrasts in isolation from the alcohol-approach bias interaction of drink type (alcohol *vs* soft drinks) \times movement (approach *vs* avoid). Namely, there are methodological reasons to include a neutral category (soft drinks) to the main analysis. First, this allowed us to correct for general approach/avoid tendencies. For example, it may be that patients generally show reduced BOLD responses for approach tendencies of neutral stimuli, such as soft drinks. Second, this corrects for differences in visual feedback and motor movements between approach (zoom in/pull) and avoidance (zoom out/push) trials. Third, defining automatic drug biases as the difference between BOLD signals elicited by drug cues and neutral cues is in line with previous fMRI research on the drug approach bias (Cousijn *et al*, 2012), the drug attentional bias (Janes *et al*, 2010; Vollstadt-Klein *et al*, 2012), and drug-cue reactivity (Beck *et al*, 2012; Childress *et al*, 1999; Grusser *et al*, 2004; Heinz *et al*, 2004, 2009; Wrase *et al*, 2007). Nevertheless, the between-group differences in the soft-drink-approach tendency contrast rather than for alcohol may well be meaningful. It may be that the alcohol-approach bias is due to decreased motivational brain responses to naturally rewarding stimuli, such as soft drinks, rather than an increased motivational response to alcohol. This is in line with previous studies showing that addicted individuals demonstrate reduced reward-related activation to naturally rewarding stimuli compared with controls (Volkow *et al*, 2004; Wrase *et al*, 2007). In previous fMRI research on drug-approach biases, drug-attentional biases and drug-cue reactivity *post-hoc* tests exploring interactions have not usually been performed (for an exception, see Braus *et al*, 2001), nor have plots of the separate β -coefficients of alcohol/neutral subscores been provided (Beck *et al*, 2012; Childress *et al*, 1999; Cousijn *et al*, 2012; Grusser *et al*, 2004; Heinz *et al*, 2004; Janes *et al*, 2010; Wrase *et al*, 2007; Vollstadt-Klein *et al*, 2012). Therefore, future fMRI studies should assess in detail whether increased alcohol cue-evoked reactivity is indeed due to enhanced reactivity to alcohol cues, or rather

(or additionally) due to reduced reactivity to natural rewards. This could have implications for treatment: rather than attempting to reduce the appeal of alcohol, one could promote the appeal of naturally rewarding stimuli.

A few limitations of the present study need to be mentioned. First, the duration of abstinence of patients varied between 1 week and 6 months, which may have influenced craving and automatic processes. However, length of abstinence was neither negatively correlated with BOLD responses in our ROIs in the approach-alcohol contrast, nor with BOLD responses in the dlPFC in the avoid-alcohol contrast. Therefore, alcohol-approach-bias-related brain responses may be independent of abstinence and could hence have a significant role in relapse even after long-term abstinence. Second, there were more smokers in the alcohol-dependent group than in the healthy control group. An exploratory analysis revealed that when including smoking behavior as a covariate, mPFC activity did not reach significance ($p > 0.05$, FWE). Hence, it cannot be excluded that the mPFC effects were due to smoking rather than alcohol dependence or to the combination of both addictive behaviors. However, this is unlikely, as our task was exclusively focused on responses to alcohol and soft-drink cues rather than smoking cues. Moreover, smoking behavior was highly correlated with alcohol use and craving in patients. Consequently, including smoking as a covariate may remove variance explained by drinking behavior. Furthermore, although smoking generally influences BOLD (Jacobsen *et al*, 2002), contrasting approach versus avoid trials made the results independent of general differences in BOLD response due to nicotine use.

In summary, our findings suggest that the automatic alcohol-approach bias is related to changes in the motivational system in alcohol-dependent patients. Even when patients express an explicit wish to remain abstinent, reflexive embodied reactions to alcohol and motivational brain mechanisms are likely to make patients vulnerable for relapse. The findings have implications for treatment of alcohol addiction. Treatment generally focuses on the improvement of conscious control (cognitive behavioral therapy or counseling) and reduction of craving by pharmacotherapy. However, our current results and recent clinical effects of bias modification training (Eberl *et al*, 2012; Wiers *et al*, 2011) suggest the automatic drug approach bias as a potential target for clinical intervention. Future studies should focus on whether and how training influences addictive brain states.

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